WHAT IS CLAIMED IS:

1. An antibody that immunospecifically binds to BLyS comprising a first amino acid sequence at least 95% identical to an second amino acid sequence selected from the group consisting of:

(a) an amino acid sequence comprising the amino acid sequence of a VHCDR of any one of the scFvs of SEQ ID NOS:1 through 2128; and

(b) an amino acid sequence comprising the amino acid sequence of a VLCDR of any one of the scFvs of SEQ ID NOS:1 through 2128.

2. The antibody of claim 1, wherein the second amino acid sequence consists of the amino acid sequence of a VHCDR3 of any one of the scFvs of SEQ ID NOS:2129 through 3227.

3. The antibody of claim 1, wherein the second amino acid sequence consists of the amino acid sequence of a VH domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

4. The antibody of claim 3 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1 through 1562.

5. The antibody of claim 4 in which said antibody immunospecifically binds to both the soluble form and membrane-bound form of BLyS.

6. The antibody of claim 4 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1 through 46 and 321 through 329.

7. The antibody of claim 6 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 2, 9, and 327.

8. The antibody of claim 4 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 834 through 872.

9. The antibody of claim 3 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1563 through 1880.

10. The antibody of claim 9 in which, and in which said antibody immunospecifically binds to the soluble form of BLyS.

11. The antibody of claim 9 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1563 through 1569.

12. The antibody of claim 9 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1570 through 1595.

13. The antibody of claim 3 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1881 through 2128.

14. The antibody of claim 13 in which said antibody immunospecifically binds to the membrane-bound form of BLyS.

15. The antibody of claim 13 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1881 through 1885.

16. The antibody of claim 13 in which said VH domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 1886 through 1908.

17. The antibody of claim 1, wherein the second amino acid sequence consists of the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

18. The antibody of claim 17 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1 through 1562.

19. The antibody of claim 18 in which said antibody immunospecifically binds to both the soluble form and membrane-bound form of BLyS.

20. The antibody of claim 18 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1 through 46 and 321 through 329.

21. The antibody of claim 20 in which said VL domain consists of the amino acid sequence of the VH domain of any one of the scFvs of SEQ ID NOS: 2, 9, and 327.

22. The antibody of claim 18 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 834 through 872.

23. The antibody of claim 17 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1563 through 1880.

24. The antibody of claim 23 said antibody immunospecifically binds to the soluble form of BLyS.

25. The antibody of claim 23 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1563 through 1569.

26. The antibody of claim 23 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1570 through 1595.

27. The antibody of claim 17 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1881 through 2128.

28. The antibody of claim 27 in which said antibody immunospecifically binds to the membrane-bound form of BLyS.

29. The antibody of claim 27 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1881 through 1885.

30. The antibody of claim 27 in which said VL domain consists of the amino acid sequence of the VL domain of any one of the scFvs of SEQ ID NOS: 1886 through 1908.

31. The antibody of claim 3, which also comprises an amino acid sequence at least 95% identical to the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

32. The antibody of claim 31, wherein the VH and VL domains are from the same scFv.

33. The antibody of claim 32, wherein the scFv is the scFv of SEQ ID NO:2.

34. The antibody of claim 32, wherein the scFv is the scFv of SEQ ID NO:9.

35. The antibody of claim 32, wherein the scFv is the scFv of SEQ ID NO:327.

36. The antibody of claim 1 wherein the first amino acid sequence is identical to the second amino acid sequence.

37. The antibody of claim 36 wherein the second amino acid sequence consists of the amino acid sequence of a VH domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

38. The antibody of claim 36 wherein the second amino acid sequence consists of the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

39. The antibody of claim 37 which also comprises an amino acid sequence 100% identical to the amino acid sequence of a VL domain of any one of the scFvs of SEQ ID NOS:1 through 2128.

40. The antibody of claim 39, wherein the scFv is the scFv of SEQ ID NO:2.

41. The antibody of claim 39, wherein the scFv is the scFv of SEQ ID NO:9.

42. The antibody of claim 39, wherein the scFv is the scFv of SEQ ID NO:327.

43. The antibody of claim 1, wherein the BLyS is a BLyS homotrimer.

44. The antibody of claim 43, wherein the individual protein components of the BLyS homotrimer consist of the mature form of BLyS.

45. The antibody of claim 1, wherein the BLyS is a BLyS heterotrimer.

46. The antibody of claim 45, wherein the BLyS heterotrimer comprises at least one BLyS polypeptide and at least one APRIL polypeptide.

47. The antibody of claim 46, wherein the BLyS polypeptide consists of the mature form of BLyS and the APRIL polypeptide consists of the mature form of APRIL.

48. The antibody of claim 1, wherein the antibody is selected from the group consisting of:

(a) a whole immunoglobulin molecule;
(b) an scFv;
(c) a monoclonal antibody;
(d) a human antibody;
(e) a chimeric antibody;
(f) a humanized antibody;
(g) a Fab fragment;
(h) an Fab' fragment;
(i) an F(ab')2;
(j) an Fv; and
(k) a disulfide linked Fv.

49. The antibody of claim 3 or 37, which also comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:

(a) a human IgM constant domain;
(b) a human IgG1 constant domain;
(c) a human IgG2 constant domain;
(d) a human IgG3 constant domain;

(e) a human IgG4 constant domain; and

(f) a human IgA constant domain.

50. The antibody of claim 17 or 38, which also comprises a light chain immunoglobulin constant domain slecetd from the group consisting of:

(a) a human Ig kappa constant domain;

(b) a human Ig lambda constant domain.

51. The antibody of claim 1, wherein the antibody has a dissociation constant (K_D) selected from the group consisting of:

(a) a dissociation constant (K_D) between 10^{-7} M and 10^{-8} M;

(b) a dissociation constant (K_D) between 10^{-8} M and 10^{-9} M;

(c) a dissociation constant (K_D) between 10^{-9} M and 10^{-10} M;

(d) a dissociation constant (K_D) between 10^{-10} M and 10^{-11} M;

(e) a dissociation constant (K_D) between 10^{-11} M and 10^{-12} M; and

(f) a dissociation constant (K_D) between 10^{-12} M and 10^{-13} M.

52. The antibody of claim 1, wherein the antibody is conjugated to a detectable label.

53. The antibody of claim 52, wherein the detectable label is a radiolabel.

54. The antibody of claim 53, wherein the radiolabel is ^{125}I, ^{131}I, ^{111}In, ^{90}Y, ^{99}Tc, ^{177}Lu, ^{166}Ho, or ^{153}Sm.

55. The antibody of claim 52, wherein the detectable label is an enzyme, a fluorescent label, a luminescent label, or a bioluminescent label.

56. The antibody of claim 1, wherein the antibody is biotinylated.

57. The antibody of claim 1, wherein the antibody is conjugated to a therapeutic or cytotoxic agent.

58. The antibody of claim 57, wherein the therapeutic or cytotoxic agent is selected from the group consisting of:

(a) an anti-metabolite,

(b) an alkylatingagent;

(c) an antibiotic;

(d) a growth factor;

(e) a cytokine;

(f) an anti-angiogenic agent;

(g) an anti-mitotic agent;

(h) an anthracycline;

(i) toxin; and

(j) an apoptotic agent.

59. An antibody of claim 1, that neutralizes BLyS or a fragment thereof.

60. The antibody of claim 59, that diminishes or abolishes the ability of BLyS or a fragment thereof to bind to its receptor.

61. The antibody of claim 60, wherein the receptor is TACI.

62. The antibody of claim 60, wherein the receptor is BCMA.

63. The antibody of claim 59, that diminishes or abolishes the ability of BLyS or a fragment thereof to stimulate B cell proliferation.

64. The antibody of claim 59, that diminishes or abolishes the ability of BLyS or a fragment thereof to stimulate immunoglobulin secretion by B cells.

65. An antibody of claim 1, that enhances the activity of BLyS or a fragment thereof.

66. The antibody of claim 65, that increases the ability of BLyS or a fragment thereof to bind to its receptor.

67. The antibody of claim 66, wherein the receptor is TACI.

68. The antibody of claim 66, wherein the receptor is BCMA.

69. The antibody of claim 65, that increases the ability of BLyS or a fragment thereof to stimulate B cell proliferation.

70. The antibody of claim 65, that increases the ability of BLyS or a fragment thereof to stimulate immunoglobulin secretion by B cells.

71. The antibody of claim 1 covalently linked to a heterologous polypeptide.

72. The antibody of claim 71, wherein the heterologous polypeptide is human serum albumin.

73. The antibody of claim 1 in a pharmaceutically acceptable carrier.

74. A kit comprising the antibody of claim 1.

75. An isolated nucleic acid molecule encoding the antibody of claim 1.

76. A vector comprising the isolated nucleic acid molecule of claim 75.

77. The vector of claim 76 which also comprises a nucleotide sequence which regulates the expression of the antibody encoded by the nucleic acid molecule.

78. A host cell comprising the nucleic acid molecule of claim 77.

79. A cell line engineered to express the antibody of claim 1.

80. An antibody that binds the same epitope as the antibody of claim 1.

81. An antibody that competitively inhibits the binding of the antibody produced by the cell line having ATCCDeposit Number PTA-3239.

82. An antibody that competitively inhibits the binding of the antibody produced by the cell line having ATCCDeposit Number PTA-3240

83. An antibody that competitively inhibits the binding of the antibody produced by the cell line having ATCCDeposit Number PTA-3243.

84. An second antibody that reduces the binding of the antibody of claim 1 by a an increment within a percentage range selected from the group consisting of:

(a) from 50% up to 60%;

(b) from 60% up to 70%;

(c) from 70% up to 80%;

(d) from 80% up to 90%; and

(e) from 90% up to 100%.

85. An antibody that immunospecifically binds to BLyS, said antibody comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH domain of an scFv comprising an amino acid sequence of any one of SEQ ID NOS: 1 to 2128.

86. An antibody that immunospecifically binds to BLyS, said antibody comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VL domain from an scFv comprising an amino acid sequence of any one of SEQ ID NOS: 1 to 2128.

87. A method for detecting aberrant expression of BLyS protein, comprising:

(a) assaying the level of BLyS expression in a first biological sample of an individual using one or more antibodies or fragments or variants thereof of claim 1; and

(b) comparing the level of BLyS assayed in biological sample with a standard level of BLyS expression or level of BLyS in a second, normal biological sample;

(c) wherein an increase or decrease in the assayed level of BLyS in the first biological sample compared to the standard level of BLyS expression or level of BLyS in a second, normal biological sample, is indicative of aberrant expression.

the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria).

[0449] In a specific embodiment, compositions of the invention may be administered to patients as vaccine adjuvants. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from an immune-deficiency. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from HIV.

[0450] In a specific embodiment, compositions of the invention may be used to increase or enhance antigen-specific antibody responses to standard and experimental vaccines. In a specific embodiment, compositions of the invention may be used to enhance seroconversion in patients treated with standard and experimental vaccines. In another specific embodiment, compositions of the invention may be used to increase the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination.

[0451] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of BLyS to a BLyS receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0452] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of BLyS to BLyS receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and

anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0453] In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of BLyS to a BLyS receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

[0454] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell responsiveness to pathogens.

[0455] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[0456] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to induce higher affinity antibodies.

[0457] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to increase serum immunoglobulin concentrations.

[0458] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to accelerate recovery of immunocompromised individuals.

[0459] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among aged populations.

[0460] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific

embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[0461] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy. B cell immunodeficiencies that may be ameliorated or treated by administering the antibodies and/or compositions of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic alymphoplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

[0462] In a specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate selective IgA deficiency.

[0463] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate ataxia-telangiectasia.

[0464] In another specific embodiment antibodies and/or compositions of the invention are administered to treat or ameliorate common variable immunodeficiency.

[0465] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked agammaglobulinemia.

[0466] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate severe combined immunodeficiency (SCID).

[0467] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate Wiskott-Aldrich syndrome.

[0468] In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked Ig deficiency with hyper IgM.

[0469] As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0470] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

[0471] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a regulator of antigen presentation by monocytes, dendritic cells, T cells and/or B-cells. In one embodiment, antibody polypeptides or polynucleotides enhance antigen presentation or antagonize antigen presentation in vitro or in vivo. Moreover, in related embodiments, this enhancement or antagonization of antigen presentation may be useful in anti-tumor treatment or to modulate the immune system.

[0472] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a mediator of mucosal immune responses. The expression of

BLyS on monocytes, the expression of BLyS receptor on B cells, and the responsiveness of B cells to BLyS suggests that it may be involved in exchange of signals between B cells and monocytes or their differentiated progeny. This activity is in many ways analogous to the CD40-CD154 signalling between B cells and T cells. Anti-BLyS antibodies and compositions of the invention may therefore be good regulators of T cell independent immune responses to environmental pathogens. In particular, the unconventional B cell populations (CD5+) that are associated with mucosal sites and responsible for much of the innate immunity in humans may respond to antibodies or compositions of the invention thereby enhancing or inhibiting individual's immune status.

[0473] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0474] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly, their susceptibility profile would likely change.

[0475] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a monocyte cell specific binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

[0476] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a B cell specific binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

[0477] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting monocytic cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

[0478] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting B-lineage cells by virtue of its specificity.

This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

[0479] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable immunodeficiency.

[0480] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a monocyte selection device the function of which is to isolate monocytes from a heterogeneous mixture of cell types. Antibodies of the invention could be coupled to a solid support to which monocytes would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

[0481] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a B cell selection device the function of which is to isolate B cells from a heterogeneous mixture of cell types. Antibodies of the invention (that do not inhibit BLyS/BLyS Receptor interaction) binding soluble BLyS could be coupled to a solid support to which B cells would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

[0482] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

[0483] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

[0484] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an antigen for the generation of antibodies to inhibit or enhance BLyS mediated responses.

[0485] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0486] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recovery.

[0487] In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of regulating secreted cytokines that are elicited by BLyS and/or BLyS receptor.

[0488] Antibody polypeptides or polynucleotides of the invention may be used to modulate IgE concentrations in vitro or in vivo.

[0489] Additionally, antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

[0490] In a specific embodiment, antibody polypeptides or polynucleotides of the invention, are administered to treat, prevent, diagnose, and/or ameliorate selective IgA deficiency.

[0491] In another specific embodiment antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate ataxia-telangiectasia.

[0492] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate common variable immunodeficiency.

[0493] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked agammaglobulinemia.

[0494] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate severe combined immunodeficiency (SCID).

[0495] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate Wiskott-Aldrich syndrome.

[0496] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM. In a specific embodiment antibody polypeptides or

polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM.

[0497] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, and/or diagnose chronic myelogenous leukemia, acute myelogenous leukemia, leukemia, hystiocytic leukemia, monocytic leukemia (e.g., acute monocytic leukemia), leukemic reticulosis, Shilling Type monocytic leukemia, and/or other leukemias derived from monocytes and/or monocytic cells and/or tissues.

[0498] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukemoid reaction, as seen, for example, with tuberculosis.

[0499] In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukocytosis, monocytic leukopenia, monocytopenia, and/or monocytosis.

[0500] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose monocyte disorders and/or diseases, and/or conditions associated therewith.

[0501] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose primary B lymphocyte disorders and/or diseases, and/or conditions associated therewith. In one embodiment, such primary B lymphocyte disorders, diseases, and/or conditions are characterized by a complete or partial loss of humoral immunity. Primary B lymphocyte disorders, diseases, and/or conditions associated therewith that are characterized by a complete or partial loss of humoral immunity and that may be prevented, treated, detected and/or diagnosed with compositions of the invention include, but are not limited to, X-Linked Agammaglobulinemia (XLA), severe combined immunodeficiency disease (SCID), and selective IgA deficiency.

[0502] In a preferred embodiment antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with any one or more of the various mucous membranes of the body. Such diseases or disorders include, but are not limited to, for example, mucositis, mucoclasis, mucocolitis, mucocutaneous leishmaniasis (such as, for example, American

leishmaniasis, leishmaniasis americana, nasopharyngeal leishmaniasis, and New World leishmaniasis), mucocutaneous lymph node syndrome (for example, Kawasaki disease), mucoenteritis, mucoepidermoid carcinoma, mucoepidermoid tumor, mucoepithelial dysplasia, mucoid adenocarcinoma, mucoid degeneration, myxoid degeneration; myxomatous degeneration; myxomatosis, mucoid medial degeneration (for example, cystic medial necrosis), mucolipidosis (including, for example, mucolipidosis I, mucolipidosis II, mucolipidosis III, and mucolipidosis IV), mucolysis disorders, mucomembranous enteritis, mucoenteritis, mucopolysaccharidosis (such as, for example, type I mucopolysaccharidosis (i.e., Hurler's syndrome), type IS mucopolysaccharidosis (i.e., Scheie's syndrome or type V mucopolysaccharidosis), type II mucopolysaccharidosis (i.e., Hunter's syndrome), type III mucopolysaccharidosis (i.e., Sanfilippo's syndrome), type IV mucopolysaccharidosis (i.e., Morquio's syndrome), type VI mucopolysaccharidosis (i.e., Maroteaux-Lamy syndrome), type VII mucopolysaccharidosis (i.e, mucopolysaccharidosis due to beta-glucuronidase deficiency), and mucosulfatidosis), mucopolysacchariduria, mucopurulent conjunctivitis, mucopus, mucormycosis (i.e., zygomycosis), mucosal disease (i.e., bovine virus diarrhea), mucous colitis (such as, for example, mucocolitis and myxomembranous colitis), and mucoviscidosis (such as, for example, cystic fibrosis, cystic fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocystic disease of the pancreas, mucoviscidosis, and viscidosis). In a highly preferred embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose mucositis, especially as associated with chemotherapy.

[0503] In a preferred embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with sinusitis.

[0504] An additional condition, disease or symptom that can be treated, prevented, and/or diagnosed by antibody polypeptides or polynucleotides of the invention is osteomyelitis.

[0505] An additional condition, disease or symptom that can be treated, prevented, and/or diagnosed by antibody polypeptides or polynucleotides of the invention is endocarditis.

[0506] All of the above described applications as they may apply to veterinary

medicine.

[0507] Antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose diseases and disorders of the pulmonary system (e.g., bronchi such as, for example, sinopulmonary and bronchial infections and conditions associated with such diseases and disorders and other respiratory diseases and disorders. In specific embodiments, such diseases and disorders include, but are not limited to, bronchial adenoma, bronchial asthma, pneumonia (such as, e.g., bronchial pneumonia, bronchopneumonia, and tuberculous bronchopneumonia), chronic obstructive pulmonary disease (COPD), bronchial polyps, bronchiectasia (such as, e.g., bronchiectasia sicca, cylindrical bronchiectasis, and saccular bronchiectasis), bronchiolar adenocarcinoma, bronchiolar carcinoma, bronchiolitis (such as, e.g., exudative bronchiolitis, bronchiolitis fibrosa obliterans, and proliferative bronchiolitis), bronchiolo-alveolar carcinoma, bronchitic asthma, bronchitis (such as, e.g., asthmatic bronchitis, Castellani's bronchitis, chronic bronchitis, croupous bronchitis, fibrinous bronchitis, hemorrhagic bronchitis, infectious avian bronchitis, obliterative bronchitis, plastic bronchitis, pseudomembranous bronchitis, putrid bronchitis, and verminous bronchitis), bronchocentric granulomatosis, bronchoedema, bronchoesophageal fistula, bronchogenic carcinoma, bronchogenic cyst, broncholithiasis, bronchomalacia, bronchomycosis (such as, e.g., bronchopulmonary aspergillosis), bronchopulmonary spirochetosis, hemorrhagic bronchitis, bronchorrhea, bronchospasm, bronchostaxis, bronchostenosis, Biot's respiration, bronchial respiration, Kussmaul respiration, Kussmaul-Kien respiration, respiratory acidosis, respiratory alkalosis, respiratory distress syndrome of the newborn, respiratory insufficiency, respiratory scleroma, respiratory syncytial virus, and the like.

[0508] In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose chronic obstructive pulmonary disease (COPD).

[0509] In another embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose fibroses and conditions associated with fibroses, including, but not limited to, cystic fibrosis (including such fibroses as cystic fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocystic disease of the pancreas, mucoviscidosis, and viscidosis), endomyocardial fibrosis, idiopathic retroperitoneal fibrosis, leptomeningeal fibrosis, mediastinal fibrosis, nodular

subepidermal fibrosis, pericentral fibrosis, perimuscular fibrosis, pipestem fibrosis, replacement fibrosis, subadventitial fibrosis, and Symmers' clay pipestem fibrosis.

[0510] In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate infectious diseases. Infectious diseases include diseases associated with yeast, fungal, viral and bacterial infections. Viruses causing viral infections which can be treated or prevented in accordance with this invention include, but are not limited to, retroviruses (*e.g.*, human T-cell lymphotrophic virus (HTLV) types I and II and human immunodeficiency virus (HIV)), herpes viruses (*e.g.*, herpes simplex virus (HSV) types I and II, Epstein-Barr virus, HHV6-HHV8, and cytomegalovirus), arenavirues (*e.g.*, lassa fever virus), paramyxoviruses (*e.g.*, morbillivirus virus, human respiratory syncytial virus, mumps, and pneumovirus), adenoviruses, bunyaviruses (*e.g.*, hantavirus), cornaviruses, filoviruses (*e.g.*, Ebola virus), flaviviruses (*e.g.*, hepatitis C virus (HCV), yellow fever virus, and Japanese encephalitis virus), hepadnaviruses (*e.g.*, hepatitis B viruses (HBV)), orthomyoviruses (*e.g.*, influenza viruses A, B and C), papovaviruses (*e.g.*, papillomavirues), picornaviruses (*e.g.*, rhinoviruses, enteroviruses and hepatitis A viruses), poxviruses, reoviruses (*e.g.*, rotavirues), togaviruses (*e.g.*, rubella virus), rhabdoviruses (*e.g.*, rabies virus). Microbial pathogens causing bacterial infections include, but are not limited to, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Corynebacterium diphtheriae* , *Clostridium botulinum*, *Clostridium perfringens*, *Clostridium tetani*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Klebsiella rhinoscleromotis*, *Staphylococcus aureus*, *Vibrio cholerae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Campylobacter* (Vibrio) *fetus*, *Campylobacter jejuni*, *Aeromonas hydrophila*, *Bacillus cereus*, *Edwardsiella tarda*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Salmonella typhimurium*, *Treponema pallidum*, *Treponema pertenue*, *Treponema carateneum*, *Borrelia vincentii*, *Borrelia burgdorferi*, *Leptospira icterohemorrhagiae*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Pneumocystis carinii*, *Francisella tularensis*, *Brucella abortus*, *Brucella suis*, *Brucella melitensis*, *Mycoplasma spp.*, *Rickettsia prowazeki*, *Rickettsia tsutsugumushi*, *Chlamydia spp.*, and *Helicobacter pylori*.

Gene Therapy

[0511] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of BLyS and/or its receptor, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0512] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0513] For general reviews of the methods of gene therapy, see Goldspiel *et al.*, Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy *3:87-95* (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 1 *l(5):155-215* (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[0514] In a preferred aspect, a composition of the invention comprises, or alternatively consists of, nucleic acids encoding an antibody, said nucleic acids being part of an expression vector that expresses the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra *et al.*, Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is an scFv;

alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments or variants thereof, of an antibody.

[0515] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

[0516] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, *e.g.*, by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, *e.g.*, by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, *e.g.*, PCT Publications WO 92/06 180; WO 92/22635; W092/203 16; W093/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra *et al.*, Nature 342:435-438 (1989)).

[0517] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention or fragments or variants thereof are used. For example, a retroviral vector can be used (see Miller *et al.*, Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct

packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen *et al.*, Biotherapy 6:29 1-302 (1994), which describes the use of a retroviral vector to deliver the mdr 1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes *et al.*, J. Clin. Invest. 93:644-651(1994); Klein *et al.*, Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[0518] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout *et al.*, Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld *et al.*, Science 252:431-434 (1991); Rosenfeld *et al.*, Cell 68:143- *155* (1992); Mastrangeli *et al.*, J. Clin. Invest. 91:225-234 (1993); PCT Publication W094/12649; and Wang, *et al.*, Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0519] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh *et al.*, Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0520] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0521] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, *e.g.*, Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen *et al.*, Meth. Enzymol. 217:618-644 (1993); Clin. Pharma. Ther. 29:69-92m (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0522] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (*e.g.*, hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0523] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0524] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0525] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody or fragment thereof are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and

maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 7 1:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[0526] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Utility of a Composition

[0527] The compounds of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, *in vitro* assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if an antibody or composition of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested in *in vitro* assays and animal model systems prior to administration to humans.

[0528] Antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, chicken, cows, monkeys, and rabbits. For *in vivo* testing of an antibody or composition's toxicity any animal model system known in the art may be used.

[0529] Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of an antibody or composition of the invention to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, or to prevent, ameliorate or alleviate the symptoms of disease a progression. The treatment is considered therapeutic if there is, for example, a reduction in viral load,

amelioration of one or more symptoms, or a decrease in mortality and/or morbidity following administration of an antibody or composition of the invention.

[0530] Antibodies or compositions of the invention can be tested for the ability to induce the expression of cytokines such as IFN-γ, by contacting cells, preferably human cells, with an antibody or composition of the invention or a control antibody or control composition and determining the ability of the antibody or composition of the invention to induce one or more cytokines. Techniques known to those of skill in the art can be used to measure the level of expression of cytokines. For example, the level of expression of cytokines can be measured by analyzing the level of RNA of cytokines by, for example, RT-PCR and Northern blot analysis, and by analyzing the level of cytokines by, for example, immunoprecipitation followed by western blot analysis and ELISA. In a preferred embodiment, a compound of the invention is tested for its ability to induce the expression of IFN-γζ

[0531] Antibodies or compositions of the invention can be tested for their ability to modulate the biological activity of immune cells by contacting immune cells, preferably human immune cells (*e.g.*, T-cells, B-cells, and Natural Killer cells), with an antibody or composition of the invention or a control compound and determining the ability of the antibody or composition of the invention to modulate (*i.e*, increase or decrease) the biological activity of immune cells. The ability of an antibody or composition of the invention to modulate the biological activity of immune cells can be assessed by detecting the expression of antigens, detecting the proliferation of immune cells (*i.e.*, B-cell proliferation), detecting the activation of signaling molecules, detecting the effector function of immune cells, or detecting the differentiation of immune cells. Techniques known to those of skill in the art can be used for measuring these activities. For example, cellular proliferation can be assayed by ^{3}H-thymidine incorporation assays and trypan blue cell counts. Antigen expression can be assayed, for example, by immunoassays including, but not limited to, competitive and non-competitive assay systems using techniques such as western blots, immunohistochemistry radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays and FACS analysis. The activation of signaling

molecules can be assayed, for example, by kinase assays and electrophoretic shift assays (EMSAs). In a preferred embodiment, the ability of an antibody or composition of the invention to induce B-cell proliferation is measured. In another preferred embodiment, the ability of an antibody or composition of the invention to modulate immunoglobulin expression is measured.

[0532] Antibodies or compositions of the invention can be tested for their ability to reduce tumor formation in *in vitro*, *ex vivo* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to inhibit viral replication or reduce viral load in *in vitro* and *in vivo* assays. Antibodies or compositions of the invention can also be tested for their ability to reduce bacterial numbers in *in vitro* and *in vivo* assays known to those of skill in the art. Antibodies or compositions of the invention can also be tested for their ability to alleviate of one or more symptoms associated with cancer, an immune disorder (*e.g.*, an inflammatory disease), a neurological disorder or an infectious disease. Antibodies or compositions of the invention can also be tested for their ability to decrease the time course of the infectious disease. Further, antibodies or compositions of the invention can be tested for their ability to increase the survival period of animals suffering from disease or disorder, including cancer, an immune disorder or an infectious disease. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention *in vivo*.

Therapeutic/Prophylactic Compositions and Administration

[0533] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of antibody (or fragment or variant thereof) or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, an antibody or fragment or variant thereof is substantially purified (*i.e.*, substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to, animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

[0534] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above;

additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0535] Various delivery systems are known and can be used to administer antibody or fragment or variant thereof of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or antibody fragment, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0536] In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0537] In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat *et al.*, in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler

(eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 3 17-327; see generally ibid.).

[0538] In yet another embodiment, the composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:20 1 (1987); Buchwald *et al.*, Surgery 88:507 (1980); Saudek *et al.*, N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy *et al.*, Science 228:190 (1985); During *et al.*, Ann. Neurol. 25:35 1 (1989); Howard *et al.*, J.Neurosurg. 7 1:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, *i.e.*, the brain, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

[0539] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0540] In a specific embodiment where the composition of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot *et al.*, Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0541] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an antibody or a fragment thereof, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a